Title: HETEROCYCLIC TOPOISOMERASE POISONS

In the Claims

Please amend claims 1 and 15 as follows.

1. (Currently Amended) A therapeutic method comprising inhibiting cancer cells by administering to a mammal in need of such therapy, an amount of a compound of formula I:

wherein:

R₁ and R₂ are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁-C₆)alkyl, trifluoromethoxy, halo, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkythio, (C₂-C₆)alkanoyloxy, aryl or heteroaryl; or R₁ and R₂ taken together are methylenedioxy; or R₁ and R₂ taken together with the atoms to which they are attached are benzo; wherein any aryl, heteroaryl, or benzo may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁-C₆)alkyl, trifluoromethoxy, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, (C₂-C₆)alkanoyloxy, and halo;

R₃ is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁-C₆)alkyl, trifluoromethoxy, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, (C₂-C₆)alkanoyloxy, or halo; and

 R_4 and R_5 taken together are a 3, 4, or 5 membered saturated or unsaturated chain comprising members selected from the group consisting of non-peroxide oxygen, sulfur, N(X),

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and carbon, optionally substituted by oxo; wherein each X is independently absent or is H, O, (C_1-C_6) alkyl, phenyl or benzyl; and wherein at least one of said chain members is an N-H group; or a pharmaceutically acceptable salt thereof;

provided R_4 and R_5 taken together are not -N(H)-C(H)=N-; and provided R_4 and R_5 taken together are not -N(H)-C(H)=N- substituted by oxo;

effective to inhibit said cancer cells.

- 2. (Original) The method of claim 1 wherein R_1 is hydrogen, halo, aryl or heteroaryl; wherein any aryl or heteroaryl may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxy, nitro, hydroxyl, halo (C_1-C_6) alkyl, trifluoromethoxy, and halo.
- 3. (Original) The method of claim 1 wherein R₂ is hydrogen, halo, aryl or heteroaryl; wherein any aryl or heteroaryl may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁-C₆)alkyl, trifluoromethoxy, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkylthio, (C₂-C₆)alkanoyloxy, and halo.
- 4. (Original) The method of claim 1 wherein R_1 and R_2 taken together are methylenedioxy.
- 5. (Original) The method of claim 1 wherein R_1 and R_2 taken together are benzo, which benzo is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_1-C_6) alkoxy, nitro, hydroxyl, halo (C_1-C_6) alkyl, trifluoromethoxy, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylthio, (C_2-C_6) alkanoyloxy, and halo.
 - 6. (Original) The method of claim 1 wherein R_3 is hydrogen.

- 7. (Original) The method of claim 1 wherein R₃ is (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁-C₆)alkyl, trifluoromethoxy, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio, (C₂-C₆)alkanoyloxy, or halo.
- 8. (Original) The method of claim 1 wherein R₄ and R₅ taken together are –N(H)-N=N-, -N(H)-N(H)-CH₂-, -N(H)-N(H)-CH₂-, -N(H)-CH₂-, -N(H)-C(=O)
- 9. (Original) The method of claim 1 wherein R_4 and R_5 taken together are -N(H)-N=N-, $-N(H)-CH_2-N(H)-$, $-N(H)-CH_2-CH_2-$, or $-N(H)-C(H_2-CH_2-CH_2-$).
- 10. (Previously Presented) The method of claim 1 wherein R_4 and R_5 taken together are -N(H)-N=N-, -N(H)-C(=O)-C(=O)-N(H)-, -N(H)-CH=CH-, $-N(H)-CH_2-CH_2-$, $-N(H)-CH_2-CH_2-$, or $-N(H)-CH_2-CH_2-N(H)-$.
- 11. (Original) The method of claim 1 wherein R_4 and R_5 taken together are -N(H)-N=N- or -N(H)-C(=O)-C(=O)-N(H)-.
 - 12. (Original) The method of claim 1 wherein R_1 and R_2 are not both hydrogen.

- 13. (Original) The method of claim 1 wherein R_1 and R_2 are each independently halo.
- 14. (Original) The method of claim 1 wherein R_1 and R_2 are each bromo.
- 15. (Currently Amended) A method comprising inhibiting cancer cells by contacting said cancer cells with an effective amount of a compound of formula I:

$$R_2$$
 R_3
 R_4
 R_5

wherein:

 R_1 and R_2 are each independently hydrogen, $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, $(C_1\text{-}C_6)$ alkoxy, nitro, hydroxyl, halo $(C_1\text{-}C_6)$ alkyl, trifluoromethoxy, halo, $(C_3\text{-}C_6)$ cycloalkyl $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkanoyl, hydroxy $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkoxycarbonyl, $(C_1\text{-}C_6)$ alkylthio, $(C_2\text{-}C_6)$ alkanoyloxy, aryl or heteroaryl; or R_1 and R_2 taken together with the atoms to which they are attached are benzo; wherein any aryl, heteroaryl, or benzo may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$ alkyl, $(C_3\text{-}C_6)$ cycloalkyl, $(C_1\text{-}C_6)$ alkoxy, nitro, hydroxyl, halo $(C_1\text{-}C_6)$ alkyl, trifluoromethoxy, $(C_3\text{-}C_6)$ cycloalkyl $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkanoyl, hydroxy $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkoxycarbonyl, $(C_1\text{-}C_6)$ alkylthio, $(C_2\text{-}C_6)$ alkanoyloxy, and halo;

 R_3 is hydrogen (C_1 - C_6)alkyl, (C_3 - C_6)cycloalkyl, (C_1 - C_6)alkoxy, nitro, hydroxy, halo(C_1 - C_6)alkyl, trifluoromethoxy, (C_3 - C_6)cycloalkyl(C_1 - C_6)alkyl, (C_1 - C_6)alkanoyl, hydroxy(C_1 - C_6) alkyl, (C_1 - C_6)alkoxycarbonyl, (C_1 - C_6)alkylthio, (C_2 - C_6)alkanoyloxy, or halo; and

 R_4 and R_5 taken together are a 3, 4, or 5 membered saturated or unsaturated chain comprising members selected from the group consisting of non-peroxide oxygen, sulfur, N(X),

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and carbon, optionally substituted by oxo; wherein each X is independently absent or is H, O, (C₁-C₆)alkyl, phenyl or benzyl; and wherein at least one of said chain members if an N-H group; or a pharmaceutically acceptable salt thereof;

provided R₄ and R₅ taken together are not -N(H)-C(H)=N-; and provided R₄ and R₅ taken together are not -N(H)-C(H)=N- substituted by oxo.

- 16. (Original) The method of claim 15 wherein R₁ is hydrogen, halo, aryl or heteroaryl; wherein any aryl or heteroaryl may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁- C_6)alkoxy, nitro, hydroxy, halo (C_1-C_6) alkyl, trifluoromethoxy, and halo.
- 17. (Original) The method of claim 15 wherein R₂ is hydrogen, halo, aryl or heteroaryl; wherein any aryl or heteroaryl may optionally be substituted by 1, 2, or 3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁- C_6)alkoxy, nitro, hydroxyl, halo (C_1-C_6) alkyl, trifluoromethoxy, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylthio, (C_2-C_6) alkylthio, (C_3-C_6) alkylthio, C_6)alkanoyloxy, and halo.
- 18. (Original) The method of claim 15 wherein R₁ and R₂ taken together are methylenedioxy.
- 19. (Original) The method of claim 15 wherein R_1 and R_2 taken together are benzo, which benzo is optionally substituted 1, 2, or 3 substituents independently selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, nitro, hydroxyl, halo(C₁- C_6)alkyl, trifluoromethoxy, (C_3-C_6) cycloalkyl (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, hydroxy (C_1-C_6) alkyl, trifluoromethoxy, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, hydroxy (C_1-C_6) alkyl, trifluoromethoxy, (C_3-C_6) cycloalkyl, (C_1-C_6) alkyl, (C_1-C_6) alkanoyl, hydroxy (C_1-C_6) alkyl, $(C_1-C_6$ C_6)alkyl, (C_1-C_6) alkoxycarbonyl, (C_1-C_6) alkylthio, (C_2-C_6) alkanoyloxy, and halo.
 - 20. (Original) The method of claim 15 wherein R₃ is hydrogen.

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- 21. (Original) The method of claim 15 wherein R₃ is (C₁-C₆)alkoxy, nitro, hydroxy, halo(C₁-C₆)alkyl, trifluoromethoxy, (C₁-C₆)alkanoyl, hydroxy(C₁-C₆)alkyl, (C₁- C_6)alkoxycarbonyl, (C_1-C_6) alkylthio, (C_2-C_6) alkanoyloxy, or halo.
- 22. (Original) The method of claim 15 wherein R₄ and R₅ taken together are -N(H)-CH₂-CH₂-, -N(H)-CH₂-CH₂-CH₂-, N(H)-CH₂-CH₂-CH₂-, -N(H)CH₂-CH₂-N(H)-, -N(H)CH₂-CH₂-O-, -N(H)-CH₂-CH₂-S-, -N(H)-CH₂-CH₂-CH₂-N(H)-, N(H)-CH₂-CH₂-CH₂-O-, -N(H)-CH₂-CH₂-CH₂-S-, -N(H)-CH₂-CH₂-N(H)-CH₂-, -N(H)-CH₂-CH₂-O-CH₂-, -N(H)-CH₂- CH_2-S-CH_2- , $-N(H)-C(=O)-C(=O)-CH_2-$, -N(H)-C(=O)-C(=O)-N(H)-, -N(H)-C(=O)-C(=O)-O-, -N(H)-C(=O)-C(=O)-S-, $-N(H)-C(=O)-CH_2-CH_2-$, $-N(H)-CH_2-N(H)-C(=O)-$, $-CH_2-S-CH_2-N(H)-C(=O)-$, -CH₂-N(H)-CH₂-S-, -CH₂-N(H)-CH₂-, -CH₂-CH₂-N(H)-CH₂-, -CH₂-CH₂-CH₂-N(H)-CH₂-, - $CH_2-N(H)-CH_2-CH_2-O-$, or $-CH_2-N(H)-CH_2-CH_2-S-$.
- 23. (Original) The method of claim 15 wherein R₄ and R₅ taken together are –N(H)-N=N-, -N(H)-CH₂-N(H)-, -N(H)-CH=CH-, -N(H)-CH₂-CH₂-, -N(H)-CH₂-CH₂-, -N(H)-CH₂-CH₂-CH₂-CH₂-, -N(H)-CH₂-CH₂-N(H)-, -N(H)-CH₂-CH₂-O-, -N(H)-CH₂-CH₂-S-, -N(H)- $CH_2-CH_2-CH_2-N(H)-$, $-N(H)-CH_2-CH_2-CH_2-O-$, $-N(H)-CH_2-CH_2-CH_2-CH_2-S-$, or -N(H)-C(=O)-C(=O)-N(H)-.
- 24. (Previously Presented) The method of claim 15 wherein R₄ and R₅ taken together are $-N(H)-N=N-, -N(H)-C(=O)-C(=O)-N(H)-, -N(H)-CH=CH-, -N(H)-CH_2-CH_2-, -N(H)-CH_2-CH_2 CH_{2}$ -, or $-N(H)-CH_{2}-CH_{2}-N(H)$ -.
- 25. (Original) The method of claim 15 wherein R₄ and R₅ are taken together are -N(H)-N=N- or -N(H)-C(=O)-C(=O)-N(H)-.
 - 26. (Original) The method of claim 15 wherein R_1 and R_2 are not both hydrogen.

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- 27. (Original) The method of claim 15 wherein R₁ and R₂ are each independently halo.
- 28. (Original) The method of claim 15 wherein R_1 and R_2 are each bromo.